Quick guide

Presenilins

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What are they? Presenilins (PS) have eight transmembrane domains, and a cytosolic loop which undergoes self-cleavage to generate amino- and carboxy-terminal fragments that remain associated in a high molecular weight complex. There are two *PS* genes in mammals and homologs in *Caenorhabditis elegans*, *Drosophila melanogaster*, and *Arabidopsis thaliana* but not in *Saccharomyces cerevisiae*.

Where are they found? They are localized in the endoplasmic reticulum and Golgi membranes, and have been detected at the plasma membrane. They are expressed in most cell types throughout development and in adulthood.

How did they get that name? *Presenilins* were identified as susceptibility genes for familial Alzheimer's disease.

What do they do normally? Analyses of the *C. elegans* orthologs Sel-12 and Hop-1, and of double knockout mice showed that presenilins are involved in Notch signalling and particularly in the cleavage of the trans-membrane domain of the Notch receptor after ligand binding, releasing an intracellular fragment that allows signal transduction. This activity is called γ-secretase by analogy with cleavage of the amyloid precursor protein, APP, as presenilins are involved in the proteolysis of APP. In this case, β-secretase produces a membrane-associated carboxy-terminal fragment of APP, which is cleaved by γ-secretase. The γ-secretase cleavage of both APP and Notch is facilitated by PS1 and PS2, and there is evidence that the presenilins themselves could be the proteases that mediate this event.

And in Alzheimer's disease? Amyloid β peptides 40/42 are normal products of APP metabolism. The appearance of Alzheimer's disease correlates with increased APP cleavage, and a change in the ratio of the two products which may lead to the formation of so-called senile plaques.

Other putative roles for presenilins… They may interact with cadherin–catenin complexes to modulate the canonical Wnt pathway, and participate in cell–cell contacts. They may also interact with calsenilin to modulate cellular calcium metabolism and control neuronal apoptosis. Presenilins may be required for a normal Unfolded Protein Response and may act as general regulators of apoptosis and as chaperones.

Can we do without them? No, although PS1 and PS2 are partially redundant. *PS1*$^{-/-}$ mice die shortly after birth with defects of the axial skeleton, neurogenesis and neuronal survival while *PS2*$^{-/-}$ mice show very mild defects. Mice lacking both genes have a phenotype similar to full Notch-1 deficiency, and die during early embryogenesis. On the other hand, too much presenilin is also detrimental, as in Alzheimer's disease.

Where can I find out more?

http://www.alzforum.org
Steiner H, Haas C: Intramembrane proteolysis by presenilins. *Nat Rev* 2000, 1:217-224.
Kopan R, Goate A: A common enzyme connects Notch signaling and Alzheimer's disease. *Genes Dev* 2000, 14:2799-2806.

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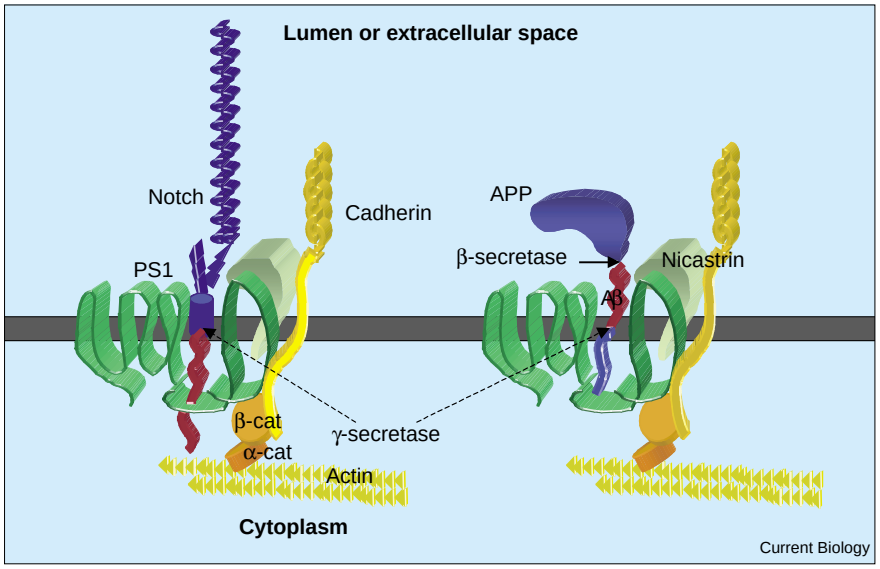

A model for presenilin-containing γ-secretase complex. Heterodimeric presenilin (green) interacts directly with the γ-secretase substrates Notch (left part) or APP (right part), and also with nicastrin (light green), cadherin (yellow) and β-catenin (β-cat, orange). The yellow- and orange-colored items represent proteins that are linked to the cytoskeleton. In red are the intracytoplasmic part of the Notch receptor and the amyloid β (Aβ) peptides derived from APP, as a result of γ-secretase activity.